Vinflunine for Non-small Cell Lung Cancer

Realistic Hopes?

To the Editor:

The enthusiasm of Tournoux-Facon et al.[1] for vinflunine for non-small cell lung cancer needs comments.

In a phase III study, vinflunine has not only showed similar efficacy end points with docetaxel but also higher rates of adverse effects in patients who have experienced treatment failure with first-line platinum-based chemotherapy.[2]

For advanced or metastatic transitional cell carcinoma of the urothelial tract, the European Medicines Agency granted a marketing authorization for vinflunine in June 2009 despite Bristol had previously said it hoped to submit the drug to the Food and Drug Administration in 2008 but gave up. However, the National Institute for Clinical Excellence (United Kingdom) has just published (March 2011) its second negative evaluation: Vinflunine is not recommended.[3] Indeed, the phase III study showed neither significant ($p = 0.29$) nor relevant (2.3 months) change in median overall survival versus best supportive care. Moreover, the incremental cost-effectiveness ratio (£126,422) was substantially more than the higher limit considered as cost-effective.

Gemcitabine is approved by the Food and Drug Administration in combination with cisplatin for the first-line treatment of patients (for whom surgery is not possible) with locally advanced (stage IIIA or IIIB) or metastatic (stage IV or cancer that has spread) non-small cell lung cancer.

The prerequisites to support the testing of vinflunine in combination with gemcitabine may be questioned.

Alain Braillon, MD, PhD
Gres. Public Health
Amiens, France

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Address for correspondence: Alain Braillon, MD, PhD, Gres, 27 rue Voiture, 80000 Amiens, France. E-mail: braillon.alain@gmail.com

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Reply to the Letter to the Editor Entitled "*Vinflunine for Non-small Cell Lung Cancer: Realistic Hopes?*"

In Reply:

In his letter to the editor, Dr. Braillon comments our "enthusiasm," which originally means inspiration or possession by the presence of a god. More modestly, the goal of our phase I study was to determine a recommended dose for vinflunine and gemcitabine.[1] Beyond this semantic remark, his editorial requires some scientific comments.

The phase III study to which Dr. Braillon refers[2] showed in fact similar efficacy end points with docetaxel, a standard treatment in second-line non-small cell lung cancer (NSCLC). Regarding tolerability, he writes that vinflunine has a "higher rate of adverse events," not mentioning that neuropathic pain, alopecia, diarrhea, and nail disorders were significantly more frequent with docetaxel. The authors of this study were slightly more accurate: "Despite higher rates of some adverse events (anemia, abdominal pain, constipation, fatigue), the overall toxicity profile of vinflunine was manageable."

Regarding vinflunine for metastatic or advanced transitional cell carcinoma of the urothelial tract after failure of a platinum-containing regimen, Dr. Braillon is absolutely right when he mentions that Bristol Myers Squibb (BMS) gave up this development in the United States. Pierre Fabre's officials explained to us that BMS made this decision based on strictly strategic reasons. BMS gave up before filing to Food and Drug Administration, while Pierre Fabre filed successfully to European Medicines Agency (EMA), which is not known for being less demanding than Food and Drug Administration. Dr. Braillon also refers to the fact that despite EMA giving marketing authorization for vinflunine on the basis of the results of the phase III study,[3] National Institute for Health and Clinical Excellence (NICE) does not recommend vinflunine in the United Kingdom. This unfavorable assessment[4] was based on the results in the intent-to-treat population and on cost-effectiveness, while EMA based their approval on the eligible population. With the same logics, NICE has also rejected the use of many other anticancer agents that benefit to numerous patients across the rest of the European Union. This is the reason why Pierre Fabre appealed NICE's decision and is still waiting for the final decision.

Dr. Braillon questions the rationale for combining vinflunine and gemcitabine in first-line NSCLC. Vinflunine has showed an activity in second-line NSCLC similar to that of docetaxel, a standard treatment. The combination of cisplatin and vinflunine in first-line NSCLC showed interesting results.[5] Vinflunine acting on M and G2 phases and gemcitabine on S phase, we considered that combining these two agents might enhance their cytotoxic potential in first-line NSCLC.

Jean-Marc Tourani, MD, PhD
Centre Hospitalier Universitaire–Pôle Régional de Cancérologie
Poitiers, France

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Address for correspondence: Jean-Marc Tourani, MD, PhD, Centre Hospitalier Universitaire–Pôle, Régional de Cancérologie, Poitiers, France. E-mail: marie.claire.pinel@pierre-fabre.com

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Primary Cardiac Angiosarcoma with Good Response to Paclitaxel

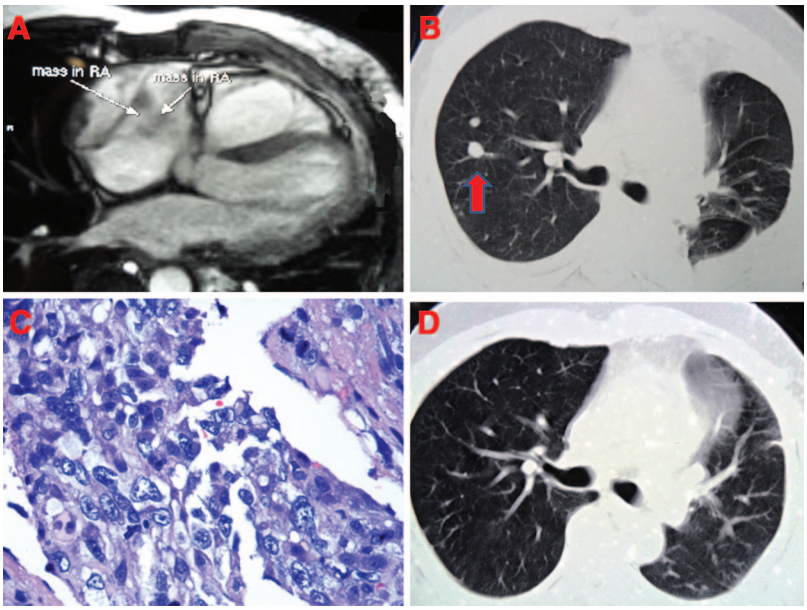

FIGURE 1. *A*, Magnetic resonance image of the heart at baseline showing a mass lesion in the right atrium. *B*, Contrast-enhanced computed tomography (CT) scan of the chest before treatment showing multiple lung metastasis in the right lower lobe (red arrow). *C*, Hematoxylin & eosin section (×400) of the biopsy specimen showing ill-defined vascular channels lined by atypical endothelial cells. *D*, Contrast-enhanced CT scan of the chest posttreatment showing complete resolution of lung metastasis.

To the Editor:

With reference to two recently published reports on cardiac angiosarcoma[1,2] wherein both patients had durable response to concurrent chemoradiotherapy, we present a case of right atrial metastatic angiosarcoma who had a durable response to paclitaxel alone without radiotherapy.

A 48-year-old male developed acute onset dyspnea; on evaluation, he had hemorrhagic pericardial effusion with cardiac tamponade. After urgent pericardiocentesis, he was initially presumptively treated with antitubercular therapy for 5 months. He required multiple pericardiocentesis and underwent pleuropericardial window surgery. Follow-up echocardiogram revealed right atrial tumor invading the pericardium which was confirmed on magnetic resonance imaging (Figure 1*A*) and transesophageal echocardiogram. Chest computerized tomogram additionally revealed bilateral pleural effusion and bilateral pulmonary metastases (Figure 1*B*). Tumor biopsy by percutaneous transfemoral route showed a malignant tumor with vascular channels lined by atypical endothelial cells (Figure 1*C*) which were positive for CD31 and CD34. The patient was then referred to our institute when he was in Eastern Cooperative Oncology Group performance status 2 with muffled heart sounds. Biopsy and imaging were reviewed and were compatible with metastatic right atrial angiosarcoma.

He was initially treated with paclitaxel 80 mg/m^2 on day 1 and 8 every 3 weeks. After two cycles, his dyspnea improved with complete resolution of right atrial mass and reduction in number and size of lung metastases. Because of good tolerance, he received four additional cycles of paclitaxel at 80 mg/m^2 on days 1, 8, and 15 every 4 weeks. Computed tomography scan at the end of the treatment showed complete resolution of right atrial mass and lung metastasis (Figure 1*D*), and the patient is now progression-free for 16 months.

Cardiac angiosarcoma is the most common malignant tumor of heart, often arising from right atrium; 80% of them present with metastasis with median survival of 6 months. Nonmetastatic cardiac angiosarcoma has been treated with radical surgery, adjuvant chemotherapy, and radiotherapy. However, cardiac angiosarcomas are usually unresectable or disseminated at presentation, making radical excision difficult in most cases; thus, palliation and prolongation of survival remains the only option. Ifosfamide, cyclophosphamide, dacarbazine, and doxorubicin mostly in combination have been used in adjuvant or metastatic setting, but there are no clear guidelines as to which is the best regimen.

In the two articles recently published,[1,2] it was interesting to note the activity of taxanes. Concurrent radiotherapy was used in both cases and in the second case carboplatin was used additionally. Docetaxel with radiotherapy has resulted in good response with a patient being alive at 1-year follow-up.[3] Herein, we present a patient who had multiple lung metastasis and pleuropericardial effusion who responded very well to single agent paclitaxel without radiotherapy.

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Address for correspondence: Dr. Sameer Bakhshi, Department of Medical Oncology, Dr. B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India. E-mail: sambakh@hotmail.com

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